# CLINICAL UPDATE

Advances in the Treatment of Pancreatic Insufficiency

## Pancrelipase Delayed-Release Capsules for the Treatment of Pancreatic Insufficiency

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**G&H** What symptoms do clinicians typically see in patients with pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery?

**DW** Patients with pancreatic insufficiency (PI) have symptoms of maldigestion, including diarrhea, increased flatulence, and crampy abdominal pain. PI is also associated with loose stools, and patients may see oil floating in their stool, depending on their diet. Typically, symptoms of PI present following other symptoms of chronic pancreatitis—such as recurrent abdominal pain or episodes of acute pancreatitis—but sometimes symptoms of PI are the patient's presenting symptoms, especially in cases of autoimmune pancreatitis, as this disease has a more indolent course.

**G&H** How common is PI in patients with chronic pancreatitis or those who have had pancreatic surgery?

**DW** The prevalence of PI depends on the population being treated. At referral centers, the prevalence tends to be a little bit higher: In this setting, approximately 40–50% of patients with chronic pancreatitis or a history of major surgery have PI. In the general patient population, this percentage is lower, because a higher percentage of these pancreatitis patients have comparatively mild disease, unless the milder cases are missed. Clinicians are especially likely to miss a diagnosis of PI in individuals with autoimmune pancreatitis or other forms of pancreatitis that do not cause much pain, because pain is typically what draws the physician's attention to the pancreas.

**G&H** How effective is pancreatic enzyme replacement therapy in patients with PI due to chronic pancreatitis or pancreatic surgery?

**DW** Pancreatic enzyme replacement therapy (PERT) is very effective for its intended purpose. This efficacy becomes clear when considering how these enzymes are tested: Individuals who have lost almost all of their pancreatic function are given a meal with at least 100 g of fat, plus either pancreatic enzyme or placebo. Then, the amount of fat that was ingested is calculated, and the amount that passes through the body is measured in stool samples. If PERT is effective, then the ingested fat is digested and absorbed into the body. If patients receive placebo, then the fat remains undigested, passes through the digestive system, and ends up in the stool. A simple calculation called the coefficient of fat absorption (CFA) is used to evaluate fat digestion and absorption. In patients who have no pancreas, CFA values are around 60%; with effective PERT, patients can achieve a CFA value above 80%. Normal individuals have CFA values in the range of 80–90%. Therefore, from a dietary standpoint, high-quality pancreatic enzymes can replace pancreatic function well enough for an individual to have a completely normal diet. While this treatment does not address the other symptoms associated with pancreatic inflammation, it does treat pancreatic exocrine insufficiency with respect to digestion and absorption of nutrients.

**G&H** What was the impetus for developing pancrelipase delayed-release capsules?

**DW** Pancrelipase delayed-release capsules were first developed decades ago. The reason they are needed is because replacement enzymes derived from large animals—such as ground-up hog pancreas—are destroyed by stomach acid. Enteric coatings can be used to protect these enzymes from stomach acid, but the enteric-coated enzymes present 2 problems. First, if the pill is large, then the enzyme may not be released until the pill is far down into the intestine. Second, food does not pass from the stomach into the intestine all at one time; food trickles in over a period of approximately 18 hours. In a normal person who eats breakfast in the morning, then lunch, and then supper, the stomach is not empty until at least midnight; any food that is consumed empties from the stomach slowly and fairly continuously throughout the day. Thus, a pill that acts only at a single, random time (based on when it happens to pass out of the stomach) is not very effective. The solution to these problems is not only to protect the enzymes from acid, but also to put the enzyme into tiny microspheres so that the enzyme mixes with the food and empties from the stomach into the duodenum at the same rate as the food. Then, when the enteric coating comes off, the enzyme is in the right place at the right time.

**G&H** How long have pancrelipase delayed-release capsules been available?

**DW** These products have been available for a number of years. However, the US Food and Drug Administration (FDA) recently updated the classification of these products to require that manufacturers demonstrate that their products are stable and that they provide the labeled amount of enzyme. Previously, pancrelipase enzyme products varied in terms of their stability over time, and manufacturers often included more of the enzyme than the labeled amount in order to ensure that the product would deliver a sufficient amount of active enzyme after being on the shelf for several months. As a result of this overfilling, patients received very high doses of enzyme with fresh batches and lower doses with older batches. Also, these products were classified as food additives, which are not strictly regulated, so the actual amount of enzyme in these products often differed among manufacturers—from nearly twice the labeled amount to almost no active enzyme.

Because of this variability, physicians had difficulty figuring out whether the therapy they were prescribing was effective. In addition, because symptoms of PI can overlap with symptoms of other conditions, such as irritable bowel syndrome, a trial of PERT that failed to result in improvement could lead the physician to wrongly assume that the problem was something other than maldigestion. Now that the FDA has changed the classification of these products, however, all manufacturers must show both that their product is stable and that it is effective in improving the CFA of patients with severe PI. This change is of benefit to physicians who may use a short course of PERT to determine if symptoms of maldigestion are improved, since failure to improve is now unlikely to be related to failure of the prescribed medication.

**G&H** How do currently available pancrelipase delayed-release capsules differ?

**DW** I am only aware of 3 such products on the US market—Creon (Abbott), Pancreaze (Ortho-McNeil-Janssen Pharmaceuticals), and Zenpep (Eurand)—and I do not think there have been any head-to-head tests comparing these products. These new formulations must all meet the same standards regarding improvement in CFA, but that is a somewhat crude test; whether other, subtler differences exist among these products remains to be determined.

**G&H** Can you briefly describe how you evaluated Creon as a treatment for PI?

**DW** In order for any pancrelipase delayed-release capsule to be approved by the FDA, well-designed studies had to demonstrate that the product was effective for the treatment of PI. For Creon, 2 major studies were conducted: a study by Trapnell and colleagues involved children with cystic fibrosis, while a second study tested Creon in patients with PI due to chronic pancreatitis or pancreatic surgery. The second study, for which I was an investigator, was a double-blind, multicenter study with a large number of well-characterized patients. All of the food that the patients ate during the course of the study was prepared by dietitians, the consumed amount of food was recorded, and all stool passed during the test period was frozen and sent to a research laboratory for analysis. All patients had to have documented PI, defined as a CFA that was clearly abnormal (eg, fecal fat >15 g/day), in order to be included in this study.

Patients were randomized to receive either pancrelipase treatment (72,000 units of lipase per meal and 36,000 units per snack) or placebo for 7 days, during which time they consumed at least 100 g of fat per day. The primary outcome measure in this study was CFA at the end of the double-blind study period. Overall, this study demonstrated significant improvements among patients treated with pancrelipase enzyme. CFA values returned to near-normal levels, even while patients were eating a high-fat diet, and patients showed improvements

in stool frequency, stool consistency, abdominal pain, and flatulence, all of which provide evidence that maldigestion was effectively treated higher up in the gastrointestinal tract.

An important difference between this study and several previous studies is that the dosage of pancrelipase used in this study was fairly high: 72,000 lipase units per main meal versus only 20,000–40,000 units in previous studies. In my opinion, using this higher dose of pancrelipase enzyme is very important because this dose is the minimum amount that the pancreas must make before it fails. Patients who are receiving a lower dose of enzyme are not receiving appropriate nutrition. In patients who still have some capacity to produce pancreatic enzyme, a lower dose of pancrelipase might be sufficient, since only 10% of total pancreatic function is needed in order to maintain life, but clinicians still need to be careful not to undertreat patients.

### G&H How could the findings from your study impact clinical practice?

**DW** This study shows that treatment with pancrelipase delayed-release capsules can almost completely restore digestive function, so patients can eat a normal American diet with no symptoms of maldigestion, even if they have no pancreatic function or only minimal residual function. However, patients may still have symptoms from their pancreatitis or other overlapping problems that are unrelated to maldigestion.

### G&H Are there any patients in whom pancrelipase treatment would not be appropriate?

**DW** Our study only evaluated patients for 7 days, but it did not reveal any significant adverse effects that could be attributed to the product within this period. However, some patients may be allergic to pork products—although this is rare—or they may refuse treatment with pork products for religious reasons. The reason that pigs are used to produce pancrelipase is because pigs are omnivores, and a pig's pancreas produces all the enzymes necessary to digest a wide range of nutrients. Currently, there are no other sources of pancrelipase.

### G&H What further research is needed to improve the diagnosis and treatment of PI?

**DW** There are several assumptions about PI that I would like to see addressed. The first is the assumption that people with chronic pancreatitis are alcoholics. Along with several colleagues, our North American Pancreatic Study Group conducted a very careful study of over 1,000 patients with chronic pancreatitis in 20 centers in the United States, and we found that alcohol was actually responsible for less than half (44.5%) of all cases of chronic pancreatitis. Instead, most patients have pancreatitis caused by genetic factors, autoimmune disorders, or other causes; or the cases are idiopathic. Smoking was also found to be an important factor and is probably responsible for amplifying the effects of alcohol in the progression of mild pancreatic injury to advanced chronic pancreatitis.

This finding is important because patients with chronic pancreatitis are often malnourished; clinicians had assumed this malnutrition was due to alcoholism, but many of these patients may have been malnourished due to inadequate pancrelipase enzyme treatment. In fact, a study from Spain by Dominguez-Munoz and colleagues showed that treatment with higher doses of enzyme allowed normalization of various nutrition measures regardless of whether patients used alcohol. My concern is that some patients are not being treated sufficiently, and their ongoing signs and symptoms are simply assumed to be due to alcohol use, even though alcohol is not the cause of pancreatitis in the majority of patients with PI.

## Suggested Reading


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